Remarks

Applicants appreciate the thorough examination of the present application as evidenced by the Office Action mailed February 26, 2003 (the Office Action). Claims 1-26 are pending in this application. Claims 16, 22, and 23 have been withdrawn from consideration. Applicants have amended claims 1, 2, 5, 6, 9-11, 17, 18, and 24. Applicants have added new claims 30 and 31. Support for these amendments and newly added claims can be found in the specification and/or claims as originally filed. No new subject matter is believed to be added by the current Amendment.

Claims 1-15, 17-21, and 24-26 are currently under consideration. Claims 1-15, 17-21, and 24-26 stand rejected, and claim 18 stands objected to in the Office Action. The concerns raised by the Examiner are addressed below as set forth in the Office Action.

I. Priority

The Office Action asserts that the priority claim fails to provide adequate support under 35 U.S.C. § 112 for claims 2-4, 6, and 8 of the present application. Applicants respectfully disagree with this assertion. Bone morphogenetic protein (BMP), osteogenic protein (OPS), and cytokines are supported in the description of the priority document on page 8, lines 19-21, where it is taught that the compositions of the present invention can be used in combination with other chondrogenic stimulators, such as bone morphogenetic protein, to enhance and/or maintain the effects of these materials. One of ordinary skill in the art would readily comprehend the meaning of "chondrogenic stimulators" and understand that this would include within its scope BMPs, OPS and cytokines. Furthermore, BMP-2/-4/-7 is specifically disclosed in the priority document on page 12. With respect to claim 6, page 8 of the description clearly states that "those of ordinary skill in the art are familiar with various methods of formulating pharmaceutical compositions for local administration in diseases," and this passage specifically cites a journal article that describes delivery methods used for BMPs to effect bone repair and formation. As such, this language provides support for the formulations of compositions recited in claim 6. Claim 8 is supported in the priority document on page 7, line 28, where it is stated that RAR antagonists may be applied by means of a biodegradable sponge, gel or paste. As defined in the dictionary, a matrix is "a

surrounding substance within which something else is contained" (*Merriam-Webster Medical Dictionary, © 2002 Merriam-Webster, Inc.).* Thus, as would be understood by one of ordinary skill in the art, this definition would therefore include a "sponge, gel or paste."

As the Examiner is fully aware, the subject matter of the claimed invention need not be described literally, i.e. using the same terms in order for the disclosure to satisfy the description requirement (see *Manuel of Patent Examining Procedure* (M.P.E.P.) § 2163.02). Therefore Applicants respectfully submit that the priority document provides adequate support for the subject matter of claims 2-4, 6, and 8, and Applicants respectfully request that these claims be afforded the foreign priority date of November 19, 1998.

II. Information Disclosure Statement

The Office Action alleges that the Information Disclosure Statement (IDS) filed on February 15, 2002 fails to comply with 37 C.F.R. § 1.98(a)(1), which requires a list of all patent publications, or other information submitted for consideration by the Office.

Applicants have resubmitted via facsimile on March 31, 2003, the originally submitted IDS including a PTO-1449 form, listing the cited documents. Applicants believe that that previously submitted IDS complies with 37 C.F.R. §1.98(a)(1) where U.S. patent documents, foreign patent documents, and non-patent literature documents were listed on form PTO-1449 and a copy of the identified documents was provided. Applicants further believe that this submission addresses the Examiner's objection to the IDS in the current Office Action. However, if the Examiner maintains the assertion that the IDS is noncompliant with 37 C.F.R. §1.98(a)(1), Applicants respectfully request additional clarification of the Examiner's objection to the IDS.

III. Specification

The Office Action asserts that the present application does not contain an abstract of the disclosure as required by 37 C.F.R. § 1.71(b). Applicants provide herewith an abstract on a separate sheet as required by 37 C.F.R. §1.72(b).

IV. Claim Objections

The Office Action objects to claim 18 under 37 C.F.R. § 1.75(c) as being of improper dependent form. Applicants have amended claim 18 to properly depend from claim 17. Accordingly, Applicants respectfully request that this objection be withdrawn.

V. Claim Rejections Under 35 U.S.C. § 101 and 35 U.S.C. § 112, First Paragraph

Claims 9-11 stand rejected under 35 U.S.C. § 101 as not being supported by either a specific and substantial asserted utility or a well-established utility. Claims 9-11 stand rejected under 35 U.S.C. § 112, first paragraph, on the basis that one of ordinary skill in the art would not know how to use the claimed invention because the steps of the method are not asserted. To further clarify the present invention, Applicants have amended claims 9-11 to recite a method for inducing chondrogenesis and to include method steps.

Accordingly, Applicants respectfully request that clams 9-11 are supported by a specific and substantial asserted utility or a well-established utility and that one of ordinary skill in the art would know how to use the claimed invention, and respectfully request that the rejections of claim 9-11 under 35 U.S.C. § 101 and 35 U.S.C. § 112, first paragraph, be withdrawn.

VI. Claim Rejections Under 35 U.S.C. § 103

A. Legal Standard of Obviousness

Applicants note that in order to establish a *prima facie* case of obviousness, three basic criteria must be met. First, the prior art reference or combination of references must teach or suggest all the claim recitations. *See In re Wilson*, 165 U.S.P.Q. 494 (C.C.P.A. 1970). Second, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings in order to arrive at the claimed invention. *See In re Oetiker,* 24 U.S.P.Q.2d 1443, 1446 (Fed. Cir. 1992); *In re Fine*, 837 F.2d at 1074; *In re Skinner*, 2 U.S.P.Q.2d 1788, 1790 (Bd. Pat. App. & Int. 1986). Third, there must be a reasonable expectation of success. *See* M.P.E.P. § 2143.

B. Rejection of Claims 1-15, 17-21, and 24-26

Claims 1-15, 17-21, and 24-26 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over WO 98/08546 to Institut National De La Sante Et De La Recherche Medicale et al. (WO 98/08546). Applicants respectfully traverse this rejection.

The presently claimed invention is directed to, among other things, a method of using RAR antagonists for inducing chondrogenesis in a vertebrate. Applicants have demonstrated that RAR antagonists can be used in compositions and methods specifically to stimulate or induce chondrogenesis in those tissues and in conditions where such is desired. One of ordinary skill in the art would acknowledge that the phrase "inducing chondrogenesis" can refer to inducing the process or processes by which cartilage is formed. This process involves the formation of chondroprogenitors from multipotential mesenchymal cells and their subsequent differentiation into chondroblasts and chondrocytes. This process is reflected in the description of cartilage formation at page 26 of the present application (and page 21 of the priority application) as involving at least two steps: 1) condensation of mesenchymal cells; and 2) differentiation of condensed mesenchyme to matrix producing chondrocytes.

RA appears to be important at two stages of the chondrogenic process. For expression of the chondroblast phenotype it is important that there is cessation of RA-signalling (i.e. activation of the pathway at this stage inhibits chondroblast differentiation). At later stages, activation of the RA signalling pathway is important for maturation of chondrocytes into hypertrophic chondrocytes. Thus, antagonists promote chondroblast differentiation early on, but inhibit chondrocyte maturation later on. This is an important distinction, as the resultant phenotypes are very different, and it is the former activity of the antagonist which the Applicants assert as being beneficial for the treatment of a variety of conditions where it is desired to form new cartilage tissue.

In many tissues, such as joints where the articular cartilage provides a low friction surface to allow mobility and acts to cushion the ends of bones, production of cartilage is the desired end result and chondrocytes remain for the life of the tissue as chondrocytes. In other tissues, cartilage formation is an intermediate step in bone formation, and after chondrogenesis is over, chondrocytes continue to mature and undergo hypertrophy, followed by mineralization of the cartilage and its eventual replacement by bone. This occurs, for

example, within the growth plate of developing humans and other mammals and allows for the growth of long bones.

In stark contrast, WO 98/08646 is directed to a composition of at least one RAR antagonist and at least one RXR agonist. This mixture is suggested for use in the treatment of cancer and inflammatory disorders that include cancers, skin disorders, and rheumatoid arthritis. Rheumatoid arthritis is an inflammatory disorder. This cited reference only proposes that the combination of the RAR antagonist and RXR agonist are useful in conditions associated with cellular hypertrophy or inflammation. As such, the combination of RAR antagonist and RXR agonist is considered specifically to reduce abnormal cellular growth or to reduce inflammation. This reference is completely silent with respect to the use of a composition of a RAR antagonist (without any agonist) for inducing chondrogenesis, that is, stimulating chondrocyte differentiation, and thus, increasing cartilage formation. Chondrogenesis is not taught anywhere in WO 98/08546. As such, this reference teaches away from the claimed invention since it requires a mixture of antagonist and agonist and further because it is applicable for completely different clinical indications. As this reference does not teach or suggest the invention as claimed in the independent claims, it cannot render these claims, or claims dependent therefrom, obvious.

C. Second Rejection of Claims 1-15, 17-21, and 24-26

Claims 1-15, 17-21 and 24-26 stand rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent 6,184,256 to Basset et al. (Basset et al.). This patent proposes compositions for differentially modulating the expression of mammalian genes comprising at least one AP1- binding site and at least one RARE. The compositions comprise RXR agonists and RAR antagonists. This reference is silent as to the use of an RAR antagonist for the stimulation of chondrogenesis or the treatment of any disorder requiring chondrogenesis for its treatment. Thus, Basset et al. fails to render the present invention obvious.

D. Rejection of Claims 2-4 and 6

Claims 2, 4 and 6 stand rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent 6,326,397 Bollag et al. (Bollag et al). This patent proposes retinoid antagonist compounds for increasing the production of IL-12 and to suppress T helper cell type 2 activity, and thus, applicability for immune disorders mediated by such activity, and more

specifically, inflammatory disorders. This reference is silent as to the use of an RAR antagonist for the stimulation of chondrogenesis or the further recitations of claims 2, 4, or 6. Thus, the proposals of this patent cannot render these claims obvious.

As noted previously, three basic criteria must be met in order to establish a *prima facie case* of obviousness. The references must teach or suggest all the claim recitations. There must be some suggestion or motivation in the references themselves, or in the knowledge generally available to one of ordinary skill in the art, to modify the reference. Finally, there must be a reasonable expectation of success. Neither WO 98/08546 nor U.S. 6,184,256 teaches or suggests, among other things, any desirability to stimulate chondrogenesis, and therefore, neither reference can render the present invention obvious.

Accordingly, Applicants respectfully submit that the claims of the present application are not obvious in view of the cited references, and respectfully request that the rejection under 35 U.S.C. § 103(a) be withdrawn.

Conclusion

In view of the foregoing remarks, Applicants respectfully request entry of this Amendment, withdrawal of the outstanding rejections to the claims, and issuance of a Notice of Allowance in due course. Any questions that the Examiner may have should be directed to the undersigned, who may be reached at (919) 854-1400.

A check in the amount of $110.00 is enclosed herewith for payment of the one-month extension of time fee. This amount is believed to be correct. However, the Commissioner is hereby authorized to charge any deficiency or credit any overpayment to Deposit Account No. 50-0220.

Respectfully submitted,

Shawna Cannon Lemon
Registration No. 53,888

CERTIFICATE OF EXPRESS MAILING

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Date of Deposit: June 26, 2003

I hereby certify that this paper or fee is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and is addressed to Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

Vickie Diane Prior

Abstract of the Disclosure

The invention provides compositions comprising an RAR antagonist for promoting chondrogenesis and methods employing such compositions for treating cartilage and associated bone abnormalities resulting from injury or disease and for *ex vivo* tissue engineering.